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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,979	JOHN ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

This Office Action is in response to Applicant's Restriction Requirement remarks filed on February 28, 2008. Claim(s) 1-7 and 23-27 are pending. Applicant's election of species of compound 2 (R, S) -Methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8- (p-tert- butylphenyl)-octanoic acid (N-butyl)amide hydrochloride and election of a disease, Alzheimer's disease, without traverse of the restriction requirement in the reply is acknowledged. The requirement is deemed proper and is therefore made FINAL. Claim(s) 1-7 and 23-27 are examined herein insofar as they read on the elected invention and species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of Alzheimer's, does not reasonably provide enablement for the prevention of Alzheimer's and the other diseases as set forth in claim 1 as recited in these claims.

The instant claims are drawn to a method for the prevention of Alzheimer's and the other diseases as set forth in claim 1. The instant specification fails to provide

information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method for the prevention of Alzheimer's or the other diseases as set forth in claim 1.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of Alzheimer's or the other diseases as set forth in claim 1 totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that the Alzheimer's or the other diseases as set forth in claim 1 will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to prevent Alzheimer's or the other diseases as set forth in claim 1, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent Alzheimer's or the other diseases as set forth in claim 1 totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing Alzheimer's or the other diseases as set forth in claim 1 totally, absolutely, or permanently.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 24, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of Alzheimer's disease, does not reasonably provide enablement for the treatment of mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, and dementia associated with cortical basal degeneration comprising administration of a therapeutically effective amount of compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all the diseases set forth in claim 1 are treatable by the compounds of formula I as described in the methods claimed.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue

experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating a subject in need thereof with a number of compounds encompassed by formula I for the treatment of an array of ailments. The nature of the invention is complex in that it encompasses the treatment of a number of ailments.

(2).Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass inhibition of any number of ailments by compounds of formula I.

(3).Guidance of the Specification:

The guidance provided by the specification pertains to in vitro and in vivo testing with reference to Alzheimer's disease.

(4).Working Examples:

Applicant provides in vitro cellular assays and in vivo models of inhibition of β-sectretase activity and production

(5).State of the Art.

The state of the art is art for Alzheimer's disease is considered low. Alzheimer's disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research, exceeded in recent years only by research into AIDS and cancer. The channel hypothesis of Alzheimer's disease proposes that the beta-amyloid peptides, which accumulate in plaques in the brain actually damage and/or kill neurons by forming ion channels. An abnormal phosphorylation of tau proteins is being investigated as one of the important events in the process leading to their aggregation. There appears to be a specific alteration of a p53- mediated intracellular pathway involved in sensing and repairing DNA damage in peripheral cells, and the role of neuronal apoptosis is under investigation. But even as of 2006, there are great unknowns relating to the links between amyloid-13 and tau, to the mechanisms that determine the selective vulnerability of defined neuronal and glial populations, and to the molecular species that cause nerve cell degeneration. Many kinds of therapies have been investigated in the past, including Hydergine-LC (actually approved by the FDA for Alzheimer's Disease, but later determined to make the disease worse), Cu/Zn chelators (or Cu and Zn homeostasis regulators), endothelin B receptor agonists, TNF inhibitors, angiotensin II receptor antagonists, ACE inhibitors, EAA agonists (including partial

agoinists), estrogens, metabotropic receptor agonists, muscarinic M2 receptor antagonists, free-radical scavengers, butyrylcholinesterase inhibitors, cholinergic agonists, potassium-channel blockers, P38 kinase inhibitors, sigma-1 Receptor Agonists, 5-HT1A receptor antagonists,), secretase stimulants, and others. From this immense body of work, only two kinds of drugs ever emerged. Four Acetylcholinesterase inhibitors were found to have some limited value: tacrine (Cognex®, no longer clinically used); donepezil (Aricept®); galantamine (Razadyne®/Reminyl®/Nivalin®) and rivastigmine (Exelon®). In addition, one voltage-dependent NMDA-antagonist, Memantine (Axura®/Akatinol®/Namenda®/Ebixa®) was also found effective. Categories of agents and techniques under investigation as of 2006 include Al3 aggregation inhibitors, assorted antioxidants, γ-Secretase modulators, γ,-Secretase inhibitors, NGF mimics, PPAR agonists, HMG-CoA reductase inhibitors (statins), Ampakines, Calcium channel blockers, GABA receptor antagonists, Glycogen synthase kinase inhibitors, Intravenous immunoglobulin, Muscarinic receptor agonists, cholinesterase inhibitors, Nicotinic receptor modulators, Passive Al3 immunization, Phosphodiesterase inhibitors, Serotonin receptor antagonists, Active Af5 immunization, NGF gene therapy, H3-receptor antagonists, NSAIDs (including NO-NSAIDs and COX-2 Inhibitors), and CB1 and CB2 cannabinoid receptor agonists. It is or course entirely possible that one or more of these will eventually be made to work. However, as can be seen by the many, many categories of drugs, which never panned out, simply being the subject of active investigation is no indication that enablement is present at that time.

The skill level in this art is so low that only Acetylcholinesterase inhibitors and NMDA-antagonists have been made to work.

(6).Predictability of the Art.

The invention is directed to inhibiting cancer cells in general. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970).

(7).The Quantity of Experimentation Necessary.

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for treating all the aliments set forth in claim 1. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of all these ailments with the numerous compounds encompassed by formula I, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again.

If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat these diseases by administration of one of the compounds of formula I within the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for treating all the ailments listed in claim 1, generally by administering the various compounds of formula I of the claims is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Göshke et al (US Patent No. 5,559,111) in view of Savaskan (Neurobiology of Aging, 2001).

Göshke teaches δ-amino-γ-hydroxy-ω-aryl-alkanoic acid amides (column 75-76, examples 78 and 79). The compounds are taught as having renin-inhibiting properties and their use as antihypertensive medicinal active ingredients (abstract; column 12, lines 36-39). Specifically, Göshke teaches that the compounds can be used in the treatment of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy post-infarction, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, anxiety states and cognitive disorders (column 13, line 65-column 14, line 6).

Göshke further teaches that the compounds can be administered to human beings (column 45, 45-47).

Göshke does not teach the administration of these compounds for the treatment of Alzheimer's disease.

Savaskan teaches the primary function of the renin-angiotensin system (RAS) is to maintain fluid homeostasis and the regulation of blood pressure. Renin, a proteolytic enzyme secreted by the kidney, acts on angiotensinogen to form the inactive decapeptide angiotensin I, which, in turn, is hydrolyzed by the angiotensin converting enzyme (ACE) to the active octapeptide angiotensin II (page 541, column 1, paragraph 1). Savaskan further teaches that the increased ACE activity may be directly responsible for cognitive impairment in AD since the enhanced formation of angiotensin II would result in increased inhibitory effect of angiotensin II on acetylcholine release. This may explain the behavioral eliciting effects of ACE inhibitors on passive avoidance and retention performance in animal models of memory function page 544, column 2, paragraph 2).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the administration δ-amino-γ-hydroxy-ω-aryl-alkanoic acid amides taught by Göshke for the treatment of Alzheimer's disease. As discussed above, Göshke teaches the amide compounds may be used to treat cognitive disorders, of which, as known in the art, Alzheimer's is one. Further motivation, provided by Savaskan, discusses evidence as to how the renin-angiotensin system can be related to Alzheimer's disease and how the administration of inhibitors of this system results in retention of memory function.

Conclusion

Claims 1-7 and 23-27 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617